1. A method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy comprising: administering to a patient undergoing cancer chemotherapy a composition consisting of an effective amount of riboflavin, an effector of the urea cycle, and the amino acids alanine, glycine, serine, taurine, threonine and valine, and a suitable solvent, diluent, or carrier.

14. A pharmaceutical composition for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy consisting of: an effective amount of riboflavin, an effector of the urea cycle, and the amino acids alanine, glycine, serine, taurine, threonine, and valine, and a suitable solvent, diluent, or carrier.

26. A method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy comprising: administering to a patient undergoing cancer chemotherapy a composition consisting of an effective amount of riboflavin, an effector of the urea cycle comprising arginine and ornithine, and the amino acids alanine, glycine, serine, threonine and valine, and a suitable solvent, diluent or carrier and optionally 3-phenylacetylamino-2,6-piperidinedione.

29. A pharmaceutical composition for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy consisting of: an effective amount of riboflavin, an effector of the urea cycle comprising arginine and ornithine, and the amino acids alanine, glycine, serine, threonine and valine, and a suitable solvent, diluent, or carrier and optionally 3-phenylacetylamino-2,6-piperidinedione.

B. Remarks Regarding the Amendments

Claims 1 and 26 have been amended to more clearly point out that the presently claimed methods include administering compositions to patients who are undergoing cancer chemotherapy. Support for these amendments are found throughout the specification and particularly on page 17, lines 8-13, and in the Examples described on pages 17-21.

Claims 1, 14, 26, and 29 were amended to point out that the instant claims are directed to methods and compositions for treating patients undergoing cancer chemotherapy with formulations that consist of an effective amount of riboflavin, an effector of the urea cycle, and the amino acids alanine, glycine, serine, taurine, threonine and valine, and a suitable solvent, diluent, or carrier and, in the case of claims 26 and 29, optionally 3-phenylacetylamino-2,6-piperidinedione. Support for the active ingredients of the formulations are found throughout the specification and particularly in the tables labeled AVA and AVB on page 8 and the table labeled AVC on page 10. Support for a suitable solvent, diluent, or carrier is found on page 11, line 10 to page 13, line 22. Support for 3-phenylacetylamino-2,6-piperidinedione is found in table labeled AVC on page 10.

The present amendments do not constitute new matter.

II. REMARKS

The Examiner has rejected claims 1-31 under 35 U.S.C. § 103(a) as being obvious with respect to U.S. Patent No. 5,719,134, issued to Schmidl et al. (the Schmidl reference). Specifically, the Examiner alleges that Schmidl teaches a dietary composition useful for providing nutrition to individuals with diseases and who are unable to consume food orally. The Examiner further alleges that the instant claims are directed to methods and compositions for treating or reducing the effects of malnutrition associated with a condition or disease and that it would have been obvious to use the nutritional composition of Schmidl to treat such effects.

The Examiner has also rejected claims 1-31 under 35 U.S.C. 103(a) as being obvious in view of U.S. Patent No. 5,550,146, issued to Acosta et al. (the Acosta reference). Specifically, the Examiner alleges that the Acosta reference discloses a nutritional composition containing vitamins and amino acids for the treatment of various metabolic diseases. The Examiner alleges that the instant claims are pharmaceutical claims with an intended use of treating or reducing the

effects of malnutrition associated with a condition or disease and that it would have been obvious, in view of the Acosta reference to utilize the nutritional compositions of Acosta to treat metabolic disorders caused by a variety of diseases or conditions, such as cancer.

Applicant respectfully traverses both rejections. The Schmidl reference and the Acosta reference are both directed to nutritional compositions containing a broad spectrum of amino acids and vitamins. The Schmidl reference is directed to nutritional support for people who are unable to orally consume or digests food because of a gastrointestinal condition such as inflammatory bowel disease, intractable diarrhea, as well as several others. *See* Schmidl, col. 1, ll. 29-35. The Acosta reference is directed to nutritional compositions for people who have one of various inherited metabolic disorders in which there is a block in a metabolic sequence, leading to a toxic accumulation of intermediary metabolic products or a deficiency of an essential metabolic product. Each formulation of the Acosta reference is particular for a specific metabolic disorder. *See* Acosta, col. 1, ll. 20-43.

Neither the Schmidl nor the Acosta reference teach or suggest methods or compositions for reducing the toxicity of chemotherapy; chemotherapy is not mentioned at all in either reference. There is nothing in either reference to suggest that the compositions described therein would be effective at relieving such toxic effects of chemotherapy. In fact, it is recognized in the art that providing additional nutrition using compositions such as those disclosed in the Schmidl and Acosta references is minimally beneficial to cancer patients under going chemotherapy and may in fact do more harm than good. For example, see Ronald L. Koretz, *Parenteral Nutrition: Is it Oncologically Logical?* JOURNAL OF CLINICAL ONCOLOGY, 2(5) 534-38 (1984), which is referenced on page 3 of the instant specification. This review article concludes that parenteral nutrition provides no dramatic therapeutic benefit in cancer patients and recommends against the

practice. Likewise, Allison J. McGeer, et al., *Parenteral Nutrition in Patients Receiving Cancer Chemotherapy*, ANNALS OF INTERNAL MEDICINE 110(9) 734-36 (1989), also referenced on page 3 of the instant specification, concludes that "the evidence suggests that parenteral nutritional support was associated with net harm, and no conditions could be defined in which such treatment appeared to be of benefit. Thus the routine use of parenteral nutrition for patients undergoing chemotherapy should be strongly discouraged . . ."

Neither the Acosta nor the Schmidl reference teach the methods and specific formulations that are claimed in the instant application and that are specifically tailored to reducing the toxic effects of cytotoxic chemotherapy in cancer patients. One of skill in the art would recognize that simply providing broad-spectrum nutritional support using the compositions taught by Schmidl and/or Acosta would not be appropriate for cancer patients because cancer cells are quite similar to normal cells with regard to their nutritional requirement. In other words, by providing the patient with the formulation of Schmidl/Acosta, one would be feeding the cancer as well as the patient.

The formulations of Schmidl/Acosta contain virtually all of the amino acids and many vitamins, many of which have been shown to stimulate cancer growth. For example, both formulations contain glutamine, which, according to the inventor, is perhaps the most important amino acid for promoting cancer growth. For example, Chance, et al., *Reduction of Tumor Growth Following Treatment with a Glutamine Antimetabolite*, LIFE SCIENCES 42(1) (1988) 87-94 (abstract attached), teaches that glutamine is an essential metabolic substrate for tumor growth.

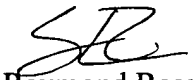
Likewise, both the Acosta and the Schmidl formulations contain folic acid, the stimulatory effect of which on cancer growth has been documented for over 60 years. In fact,

numerous chemotherapeutic agents work as anti-metabolites against folic acid. For example, Synold, et al., *Role of Folylpolyglutamate synthetase (FPGS) in Antifolate Chemotherapy; a Biochemical and Clinical Update*, LEUKEMIA & LYMPHOMA 21(1-2) (1996) 9-15 (abstract attached), points out that folate antimetabolites "continue to be the backbone of many active chemotherpeutic regimens." One of skill in the art would clearly not be motivated to provide the formulations of Acosta/Schmidl, which contain nutrients known to stimulate cancer growth, to cancer patients.

In contrast, the instantly claimed methods and compositions utilize selected amino acids and riboflavin (vitamin B-2) which reduce the toxic effect of chemotherapy and at the same time have a slight inhibitory effect on cancer. Because the cited references do not teach or suggest these aspects of the claimed invention and because the compositions of the cited references would not be suitable for the intended purpose of the presently claimed invention, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

The Examiner is invited to contact the undersigned patent agent with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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